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Elizabeth Hunt
<ehunt@adelphia.net>

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To: Rtk Chem@EPA, NCIC OPPT@EPA
cc: Leslie Scott/DC/USEPA/US@EPA, Richard Hefter/DC/USEPA/US@EPA
Subject: Dow: Submission for Sulfuric acid, diethyl ester (CAS 64-67-5) Under HPV Program

Attached is a submission on behalf of The Dow Chemical Company for Sulfuric acid, diethyl ester (CAS 64-67-5), under the US HPV Program.

This submission includes the following attached files:

- Test Plan
- IUCLID Dossier

If you have any difficulty opening these files or have any questions, please contact me.

Elizabeth Hunt



Hunt Managements Services, LLC DES_64-67-5 IUCLID 121903 FINAL.rtf



DES_64-67-5 Test Plan 121903 -FINAL.doc

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Sulfuric Acid, Diethyl Ester

(Diethyl Sulfate; CAS RN 64-67-5)

High Production Volume (HPV) Chemical Challenge Test Plan and Data Review

Prepared for:

The Dow Chemical Company

Prepared by:

Toxicology/Regulatory Services, Inc.

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December 19, 2003

**Sulfuric Acid, Diethyl Ester
(Diethyl Sulfate; CAS RN 64-67-5)
High Production Volume (HPV) Chemical Challenge
Test Plan and Data Review**

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Test Plan

Sulfuric Acid, Diethyl Ester (Diethyl Sulfate; CAS RN: 64-67-5)		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL AND CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.4	Vapor Pressure	Y	N	N	Y	N	Y	N
2.5	Partition Coefficient	Y	N	N	N	Y	Y	N
2.6	Water Solubility	Y	N	N	Y	N	Y	N
ENVIRONMENTAL FATE AND PATHWAY								
3.1.1	Photodegradation	Y	N	N	N	Y	Y	N
3.1.2	Stability in Water	Y	N	N	N	N	N	Y
3.3	Transport and Distribution	Y	N	N	N	Y	Y	N
3.5	Biodegradation	Y	N	N	Y	N	Y	N
ECOTOXICITY								
4.1	Acute Toxicity to Fish	Y	N	N	Y	N	a	a
4.2	Toxicity to Daphnia	Y	N	N	N	Y	a	a
4.3	Acute Toxicity to Algae	Y	N	N	N	Y	a	a
TOXICITY								
5.1	Acute Toxicity	Y	N	N	Y	N	Y	N
5.4	Repeated Dose Toxicity	N	N	N	N	N	N	N ^b
5.5	Genotoxicity <i>In Vitro</i> (Bacterial Test)	Y	N	N	Y	N	Y	N
5.5	Genotoxicity <i>In Vitro</i> (Mammalian Cells)	Y	N	Y	Y	N	Y	N
5.8	Reproductive Toxicity	N	N	N	N	N	N	N ^b
5.9	Development Toxicity / Teratogenicity	N	N	N	N	N	N	N ^b

a See text for discussion of ecotoxicity approach.

b DES is classified by IARC (2A; “Probably carcinogenic to humans”) and NTP (“Anticipated carcinogen”) as a carcinogen. The production, labeling and handling of DES are specifically designed to minimize exposure to carcinogenic chemicals, and are therefore considered adequate for other potential toxic hazards. See text for discussion.

**Sulfuric Acid, Diethyl Ester
(Diethyl Sulfate; CAS RN 64-67-5)
High Production Volume (HPV) Chemical Challenge
Test Plan and Data Review**

1.0 Introduction

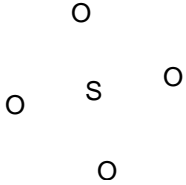
This document reviews the data availability for the High Production Volume (HPV) Chemical Challenge endpoints and provides a Test Plan for Sulfuric Acid, Diethyl Ester, hereafter called Diethyl Sulfate [DES; CAS RN 64-67-5]. DES is sponsored by The Dow Chemical Company. DES is classified as a carcinogen by IARC (2A; “Probably carcinogenic to humans”) and NTP (“Anticipated carcinogen”). As a suspect human carcinogen, exposure is strictly controlled thus eliminating the need for fulfilling some HPV endpoints (i.e. no additional precautions are required regardless of the outcome of the study). The exposure-limited testing needs are defined herein.

2.0 General Use and Exposure

Diethyl sulfate is a versatile alkylating agent for producing ethyl derivatives of many compounds such as amines, phenols, and thiols. It is used in the preparation of a wide variety of intermediates and products in surfactants, dyes, agricultural chemicals, and pharmaceuticals. The major use of diethyl sulfate is in the manufacture of quaternary ammonium salts or that are used in: textile applications for fabric softeners in detergents and for dye operations to increase the affinity of the dye for the fiber; hair care applications for shampoos, conditioners and hair spray; germicides for disinfectants and sanitizers in a broad range of products including cleaners, drilling fluids, and cooling water applications; and production of organoclays for viscosity modifiers in drilling fluids, greases, lubricants, and oil based paints, phase transfer catalysts, electroplating, emulsifying agents including asphalt additives, and corrosion inhibitors. Other uses include production of ethers from alcohols; to produce fatty acid ethyl esters for plasticizers and to alkylate substituted aniline for dyes; and as a pharmaceutical intermediate. Production in the U.S. was in the range of 0.5 to 1 million pounds in 2002.

Approximately 194 full-shift samples were collected from 1978 to 1996 at a US production site. All results ranged between none-detected (limit of detection 0.01 ppm) and 0.7 ppm. There were no results greater than the established internal exposure guideline of 1 ppm as an 8-hr TWA. Samples were collected from a variety of tasks including drumming activities, work at a loading rack, and other routine tasks. Thirty short-term samples were collected from 1975 to 1987. Results ranged from one-detected (limit of detection 0.01) to 1.8 ppm. Samples were collected during drumming operations, filter changes, and connecting and disconnecting hoses. Therefore, exposure in the workplace is considered to be of no concern and appropriate measures are taken to avoid worker contact. In addition, based on its use as a chemical intermediate and the rapid hydrolysis of any residual DES from production, no significant exposure to consumers is anticipated to occur.

3.0 General Substance Information (Identity)

Chemical Name	Sulfuric Acid, Diethyl Ester
Synonyms	Diethyl Sulfate Diaethylsulfat [German] Diethyl sulphate Diethyl tetraoxosulfate Diethylester kyseliny sirove [Czech] Ethyl sulfate
CAS Number	64-67-5
Structure	
Molecular Weight	154.18
Substance Type	Organic
Physical State	Colorless liquid
Odor	Mild
Purity	>99%

4.0 Physical/Chemical Properties

A data summary for DES is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

4.1 Melting Point

The melting point for DES is listed as -24.5 °C (CRC Press, 1975). The Material Safety Data Sheet indicates the freezing point to be -24.4 °C. These data are considered adequate to meet the HPV Chemical Challenge requirements.

4.2 Boiling Point

The boiling point for DES is listed as 208 °C (CRC Press, 1975). The Material Safety Data Sheet indicates that DES decomposes at high temperatures. These data are considered adequate to meet the HPV Chemical Challenge requirements.

4.3 Vapor Pressure

The vapor pressure for DES is listed as 0.191 hPa at 20 °C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.4 Partition Coefficient

The log K_{ow} for DES is predicted by EPIWIN to be 1.14 (U.S. EPA, 2000a). An unpublished reference from Union Carbide provides the same value (Union Carbide; unpublished data). Because of the rapid hydrolysis of DES in water (see below), this value has minimal utility in determining its environmental fate or bioaccumulation in aqueous systems. However, the low value indicates bioaccumulation is not anticipated. These data are considered adequate to meet the HPV Chemical Challenge requirements.

4.5 Water Solubility

DES rapidly hydrolyzes to ethanol and H_2SO_4 (CRC Press, 1975). A water solubility value of 7000 mg/L has been determined (McCormack and Lawes, 1983). The rate at which the hydrolysis occurs has not been adequately addressed. The value of 7000 mg/L is considered an adequate determination of water solubility for the HPV Chemical Challenge requirement and for the conduct of the water stability study (see below).

5.0 Environmental Fate

A data summary for DES is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

5.1 Photodegradation

The model prediction for atmospheric photodegradation provides a second order rate of reaction with hydroxyl radicals of $1.6 \text{ E-}12 \text{ cm}^3/\text{molecule-sec}$ and a $t_{1/2}$ of 6.5 days (U.S. EPA, 2000b). Because of the nature of use of DES, photodegradation is of minimal importance to the overall environmental fate. Degradation from accidental release to the atmosphere, however, is anticipated based on the modeling. These data are considered adequate to meet the HPV Chemical Challenge requirements.

5.2 Stability in Water

DES rapidly hydrolyzes in water with existing data (unpublished) in distilled water indicating the hydrolysis half-life at 8000 mg/L to be approximately 2 hours. Since this study was conducted at or near the maximum anticipated water solubility (guideline studies suggest using half maximum concentrations) and did not identify the hydrolysis products, it is of limited use for predicting behavior of DES in the environment. It is generally understood that the ultimate hydrolysis of DES results in the formation of ethanol and sulfuric acid. However, it is considered possible that ethyl sulfate could be a more stable intermediate. Therefore, a study to determine hydrolysis rate will be conducted following OECD Guideline 111. The concentration to be tested will be 50% of the water solubility, i.e. 3500 mg/L. It is anticipated that the preliminary test at pH 4, 7 and 9 at 50 °C will be adequate to establish the rate of hydrolysis according to the guideline; the products of hydrolysis will be determined. These data will be used to determine the need for aquatic toxicity testing as described in detail below.

5.3 Environmental Transport and Distribution

The Level III fugacity model (U.S. EPA, 2000c) was used to predict the distribution of DES released to the environment. DES is not routinely released to the environment because of the controls in place to avoid human exposure and because it is used exclusively as a chemical intermediate. Therefore, only accidental releases were considered for the fugacity modeling. Two scenarios, 100% release to air and 100% release to water were examined. For the air release the model predicted a distribution of 77% into atmosphere, 15% into water, 9% into soil, and < 0.1% into sediment. For the water release the model predicted a distribution of < 1% into atmosphere, 99% into water, < 0.1% into soil, and < 1% into sediment. These data are considered adequate to meet the HPV Chemical Challenge requirements.

5.4 Biodegradability

A study measuring the Biological Oxygen Demand provided a value of 57% degradation after 20 days (Price *et al.*, 1974). Based on this study effectively showing rapid biodegradation after 20 days along with the knowledge that rapid hydrolysis of DES occurs (see above), additional biodegradation studies are unwarranted. These data are considered adequate to meet the HPV Chemical Challenge requirements.

6.0 Ecotoxicity

A data summary for DES is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

6.1 Toxicity to Fish

Two 96 hour LC₅₀ values for DES in freshwater fish are reported; 95 mg/L for the fathead minnow (*Pimephales promelas*; Waggy and Payne, 1974) and 20 mg/L for rainbow trout (*Salmo gairdneri*; Nisso Maruzen Chemical Co., in-house data). The limited information available makes the reliability of these studies uncertain without further knowledge of the hydrolysis of DES. If hydrolysis to ethanol and sulfuric acid is completed in a short period of time (e.g. < 24 hours), these values are likely the result of sulfuric acid toxicity (LC₅₀ ~ 100 mg/L). It is proposed that the usefulness of these data be reexamined after completion of the hydrolysis testing. If complete hydrolysis occurs in less than 24 hours, these data support the conclusion that sulfuric acid is the proper test chemical and no further testing is proposed (the effects of ethanol and sulfuric acid being well understood); therefore, the available information is considered adequate to meet the HPV Chemical Challenge requirements. However, if slower hydrolysis or significant production of ethyl sulfate is indicated, an additional test with controlled timing is proposed (procedures to be determined). This study will not include analytical measurements, however, because these data are not relevant with continuous hydrolysis of the test chemical.

6.2 Toxicity to Aquatic Invertebrates

The ECOSAR model provides an EC₅₀ value for daphnia of 742 mg/L (U.S. EPA, 2000d). A similar approach to that described for fish will be used to determine the need and procedures for additional testing. If the hydrolysis of DES to ethanol and sulfuric acid is shown to be

complete, or nearly complete, in less than 24 hours, the knowledge of toxicity of sulfuric acid and ethanol is considered adequate to meet the HPV Chemical Challenge requirements.

6.3 Toxicity to Aquatic Plants

The ECOSAR model provides an EC₅₀ value for daphnia of 5.2 mg/L (U.S. EPA, 2000d). Testing may be indicated by the hydrolysis information. If the hydrolysis of DES to ethanol and sulfuric acid is shown to be complete, or nearly complete, in less than 24 hours, the knowledge of toxicity of sulfuric acid and ethanol is considered adequate to meet the HPV Chemical Challenge requirements.

7.0 Human Health-Related Data

A data summary for DES is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

7.1 Acute Toxicity

The acute oral LD₅₀ for DES is 880 mg/kg bw (Smyth *et al.*, 1949). Inhalation of DES results in an LC₅₀ between 250 (1275 mg/L) to 500 ppm (3150 mg/L) with no deaths at 250 ppm and 100% mortality at 500 ppm following four hours of exposure (Smyth *et al.*, 1949). The acute dermal LD₅₀ is 706 mg/kg/bw (Smyth *et al.*, 1951). These data are considered adequate to meet the HPV Chemical Challenge requirements.

7.2 Repeated Dose Toxicity

There are no subchronic studies available for DES. DES is classified by IARC (2A; “Probably carcinogenic to humans”) and NTP (“Anticipated carcinogen”) as a carcinogen. This classification is based on a study in which DES was administered dermally to male mice for the lifespan of the animals. Repeated dermal application of undiluted DES produced malignant skin neoplasms in 21 mice out of a surviving effective group of 27 animals (Peterson, 1979). Based on these data, the consistent mutagenic response of DES (see below) and the classification of DES as a carcinogen, the production, labeling and handling of DES are specifically designed to minimize exposure to carcinogenic chemicals. Further testing at higher doses in subchronic studies and/or identification of additional toxic responses will not alter these procedures and controls. Therefore, the available data are considered adequate to meet the HPV Chemical Challenge requirements.

7.3 Genetic Toxicity

7.3.1 *In vitro*

DES has been shown to be positive in the Salmonella preincubation reverse mutation assay (Ohtsuka and Maekawa, 1992). Although this study evaluated only one tester strain (TA100), the strong positive response precludes the need for additional testing. In this assay, DES resulted in a maximum of a 35-fold greater induction of revertants compared to the control with a clear dose response. No induction was observed at 500 µg/plate with a 6-fold increase at 1000 µg/plate and the 35-fold induction at 2000 µg/plate. DES has also been shown to be positive in mammalian cell assays. In the HGPRT mutation assay with CHO cells, a dose-related increase in induction of mutations with and without metabolic activation was observed

(Slesinski *et al.*, 1980). The maximum response varied from 8 to 35-fold induction of mutations compared to the solvent control. A sister chromatid exchange assay without metabolic activation also showed a dose-related increase in response with a maximum 2.5-fold increase in the number of SCE per chromosome (Slesinski *et al.*, 1980). In an unscheduled DNA synthesis assay, a non-dose related increase in DNA synthesis, as measured by radioactive thymidine, was observed at all concentrations ranging from 0.0001 to 0.1% (v/v) (Slesinski *et al.*, 1980). The available data are considered adequate to meet the HPV Chemical Challenge requirements.

7.3.2 *In vivo*

DES increased the incidence of micronucleated erythrocytes in a mouse micronucleus assay at one time point (48 hours) at the highest single i.p. dose (400 mg/kg) tested (Asita *et al.*, 1992). The results of a second mouse micronucleus study were also positive at 30 hours following an i.p. injection of 160 mg/kg of DES with no effect seen at 80 mg/kg (Hagashikuni and Shizuyo, 1995). A study using intrascrotal injection of DES resulted in dominant lethal effects (Malashenko, 1971). Although this study used a highly unusual dosing regimen, a second dominant lethal study is briefly reported as being positive using the more conventional intraperitoneal injection (Ehling and Neuhauser-Klaus, 1988). The available data confirm the biological activity of DES on the genome and are considered adequate to meet the HPV Chemical Challenge requirements.

7.4 Reproductive and Developmental Toxicity

There are no studies available for DES that evaluate potential reproductive or developmental toxicity. Production, labeling and handling of DES are specifically designed to minimize exposure to carcinogenic chemicals. Further testing at higher doses in studies designed to evaluate reproductive and developmental toxicity, and/or identification of positive effects in such studies, will not alter the procedures and controls currently in place for the use and handling of DES. Therefore, the available data are considered adequate to meet the HPV Chemical Challenge requirements.

8.0 Conclusion

Adequate information is available for melting point, boiling point, vapor pressure and partition coefficient for DES. Photodegradation and environmental distributions are adequately supported by the appropriate model data. Water solubility and hydrolysis will be examined in appropriate OECD guideline testing. Based on the results of these studies, the need for additional aquatic toxicity tests will be determined. If hydrolysis of DES to ethanol and sulfuric acid is complete, or nearly complete, within 24 hours, data for these daughter chemicals are considered adequate to describe the environmental hazards for DES. DES is biodegradable. In bacterial and mammalian cell systems and *in vivo* mutagenicity assays, DES is mutagenic, and it has been shown to be carcinogenic in animal studies. Based on these findings, production, labeling and handling of DES are specifically designed to minimize exposure to carcinogenic chemicals and are considered adequate for other potential toxic hazards. Additional animal testing, appropriate to meet the HPV Challenge Program requirements, will not further the understanding of DES hazard or alter current procedures for labeling and handling. Therefore, the available data are considered adequate.

9.0 References

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Table 1: HPV Data Summary

Sulfuric Acid, Diethyl Ester (Diethyl Sulfate)

CAS RN: 64-67-5		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Handbook Data (CRC)	-24.5 °C
2.2	Boiling Point		Handbook Data (CRC)	208 °C
2.4	Vapor Pressure		Handbook Data (DIPPR)	0.191 hPa (at 20 °C)
2.5	Partition Coefficient (log K _{ow})		KOWWIN v. 1.67; UCC Unpub. Data	1.14
2.6	Water Solubility		Not specified	7000 mg/L
			Handbook Data (CRC)	Decomposes to ethanol and H ₂ SO ₄ ;
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		AOPWIN v. 1.91	half-life: 6.5 days (OH Rate Constant)
3.1.2	Stability in Water		Handbook Data (CRC)	Hydrolyzes to ethanol and sulfuric acid
3.3	Transport and Distribution		Mackay Level III 100% release to air	77% into atmosphere, 15% into water, 9% into soil, < 0.1% into sediment
			Mackay Level III 100% release to water	< 1% into atmosphere, 99% into water, < 0.1% into soil, < 1% into sediment
3.5	Biodegradation		BOD20	57% after 20 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	<i>Pimephales promelas</i>	EPA/600/4-85/013 Not specified	LC ₅₀ (96 hours) = 95 mg/L LC ₅₀ (96 hours) = 20 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates	Daphnid	ECOSAR v 0.99g	EC ₅₀ (48 hours) = 742 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	Green algae	ECOSAR v 0.99g	EC ₅₀ (96 hours) = 5.2 mg/L

Table 1: HPV Data Summary
Sulfuric Acid, Diethyl Ester (Diethyl Sulfate)

CAS RN: 64-67-5		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat		LD ₅₀ : 880 mg/kg bw
5.1.2	Acute Inhalation Toxicity	Rat		LC ₅₀ (4 hr): >250 ppm (1275 mg/L); <500 ppm (3150 mg/L)
5.1.3	Acute Dermal Toxicity	Rabbit		LD ₅₀ : 706 mg/kg bw
5.4	Repeated Dose Toxicity			See Text
5.5	Genetic Toxicity <i>In Vitro</i>			
	Bacterial Test (Gene mutation)	Salmonella typhimurium TA 100 only	Ames	Positive
		CHO	HGPRT -Similar to guideline	Positive
		CHO	SCE - Similar to guideline	Positive
		Rat	Hepatocyte UDS - similar to guideline	Positive
5.6	Genetic Toxicity <i>In Vivo</i>	Mouse	Micronucleus - Similar to guideline	Positive
		Mouse	Dominant lethal	Positive
5.8	Toxicity to Reproduction / Impairment of Fertility			See Text
5.9	Developmental Toxicity / Teratogenicity			See Text

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I U C L I D

Data Set

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Existing Chemical : ID: 64-67-5
CAS No. : 64-67-5
EINECS Name : diethyl sulphate
EC No. : 200-589-6
TSCA Name : Sulfuric acid, diethyl ester
Molecular Formula : C₄H₁₀O₄S

Producer related part
Company : The Dow Chemical Company
Creation date : 12.09.2003

Substance related part
Company : The Dow Chemical Company
Creation date : 12.09.2003

Status :
Memo :

Printing date : 18.12.2003
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Flags (profile) : Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE),
Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information

Id 64-67-5
Date 18.12.2003

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	
Name	:	SIBER HEGNER RAW MATERIALS LTD.
Contact person	:	
Date	:	
Street	:	WIESENSTRASSE 8
Town	:	CH-8022 Zurich
Country	:	Switzerland
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
Flag	:	non confidential
23.10.1995		
Type	:	
Name	:	Union Carbide Benelux
Contact person	:	
Date	:	
Street	:	Norderlaan 147
Town	:	2030 Antwerpen
Country	:	Belgium
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
Flag	:	non confidential
23.10.1995		
Type	:	
Name	:	Whyte Chemicals Ltd
Contact person	:	
Date	:	
Street	:	322 Regents Park Road
Town	:	N3 2UA London
Country	:	United Kingdom
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
Flag	:	non confidential
23.10.1995		

1. General Information

Id 64-67-5
Date 18.12.2003

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : liquid
Purity : > 99 - % w/w
Colour :
Odour :

Remark : Diethyl Sulfate specification has a purity requirement of 99.5 wt %. The product as normally produced and received into the distribution system in 2002 had an average purity of 99.78 wt %. GC analysis of the storage tank for the year 2002 showed an average purity of 99.77 wt %, with a minimum and maximum purity of 99.65 and 99.87 wt %, respectively.

Source : ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

Flag : non confidential
17.12.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Diethyl Sulphate

Source : SIBER HEGNER RAW MATERIALS LTD. Zurich
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995

ethyl sulfate

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995

ETHYLSULPHATE

Source : Whyte Chemicals Ltd London
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995

1. General Information

Id 64-67-5
Date 18.12.2003

sulfuric acid, diethyl ester

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits : no
Symbols : T, , ,
Nota : E, ,
R-Phrases : (45) May cause cancer
(46) May cause heritable genetic damage
(20/21/22) Harmful by inhalation, in contact with skin and if swallowed
(34) Causes burns
S-Phrases : (53) Avoid exposure - obtain special instructions before use
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
Source : ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
Flag : non confidential
23.10.1995

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : carcinogenic, category 2
R-Phrases : (45) May cause cancer
Specific limits :
Source : ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
Flag : non confidential
23.10.1995
Classified : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (34) Causes burns
Specific limits :
Source : ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

1. General Information

Id 64-67-5
Date 18.12.2003

Flag : non confidential
23.10.1995

Classified : as in Directive 67/548/EEC
Class of danger : harmful
R-Phrases : (20/21/22) Harmful by inhalation, in contact with skin and if swallowed
Specific limits :

Source : ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

Flag : non confidential
23.10.1995

Classified : as in Directive 67/548/EEC
Class of danger : mutagenic, category 2
R-Phrases : (46) May cause heritable genetic damage
Specific limits :

Source : ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

Flag : non confidential
23.10.1995

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : .03 ml/m3

Source : SIBER HEGNER RAW MATERIALS LTD. Zurich
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995

Type of limit : TLV (US)
Limit value :

Remark : 1 ppm-skin: TLV-TWA
Union Carbide recommendation

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)

1. General Information

Id 64-67-5
Date 18.12.2003

23.10.1995

UNION CARBIDE CORPORATION Houston

Remark : 1 PPM - SKIN TWA
Source : Whyte Chemicals Ltd London
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : As the quantities of this substance placed on the EU market by Union Carbide Benelux N.V. are normally sourced from the manufacturing facilities of its U.S. parent company, no exposure can arise within the EU from the manufacture of these quantities. The comments below on exposure are restricted to uses for which Union Carbide believes its customers use this substance.

Major use(s): chemical intermediate for dyes, pharmaceuticals etc. always used in closed systems.

Sources of human exposure: negligible assuming appropriate industrial hygiene and personal protection precautions are observed. There are no consumer uses, hence no public exposure.

Sources of environmental exposure: none - this substance is chemically transformed into other substances. Releases to waste water systems hydrolyse to ethanol (inherently biodegradable) and sulphuric acid.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)

1. General Information

Id 64-67-5

Date 18.12.2003

23.10.1995

UNION CARBIDE CORPORATION Houston

Remark : Diethyl Sulfate is used for basic organic synthesis. When handling according to the basic precaution rules (avoid all possible contact with the product) no harm whether to humans nor to the environment are to be expected.

Source : SIBER HEGNER RAW MATERIALS LTD. Zurich
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

16.09.2003

Country : Germany MAK-LIST: Group IIIA2

Source : SIBER HEGNER RAW MATERIALS LTD. Zurich
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995

Remark : DES IS PRODUCED IN A CLOSED PROCESS. THE ONLY POSSIBLE EXPOSURE TO HUMANS AND ENVIRONMENT IS VIA AN ACCIDENTAL RELEASE. NO FURTHER INFORMATION AVAILABLE.

Source : Whyte Chemicals Ltd London
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

16.09.2003

1.11 ADDITIONAL REMARKS

Remark : Disposal: Incinerate in a furnace where permitted under appropriate national and local regulations. May be mixed with solvent (acetone) for ease in burning. In very dilute concentrations (about 10 ppm) in water, it may be amenable to biodegradation in a treatment plant, but the acidity resulting from hydrolysis must be carefully monitored and neutralized.

Transport: Diethyl sulphate is classified as class 6.1 product according to the ADR/RID/IMDG/ICAO regulations. Diethyl sulphate is shipped in appropriate road and rail transport units and smaller packages (e.g. drums). The product has to be loaded, unloaded or transloaded with a vapour return line. Every container used for diethyl sulphate shall have no bottom outlets. Only top-loading and unloading is allowed.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

16.09.2003

Remark : NO ADDITIONAL REMARKS.

Source : Whyte Chemicals Ltd London
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2. Physico-Chemical Data

Id 64-67-5
Date 18.12.2003

2.1 MELTING POINT

Value	:	= -24.5 - °C	
Reliability	:	(2) valid with restrictions	
Flag	:	Critical study for SIDS endpoint	
03.11.2003			(6)
Value	:	-25 - °C	
Source	:	Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995			(28)
Value	:	-24.4 - °C	
Source	:	Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995			(22) (38)

2.2 BOILING POINT

Value	:	= 208 - °C at	
Reliability	:	(2) valid with restrictions	
Flag	:	Critical study for SIDS endpoint	
03.11.2003			(6)
Value	:	208 - °C at	
Decomposition	:	yes	
Method	:		
Year	:		
GLP	:		
Test substance	:		
Source	:	Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995			(22)
Value	:	209.5 - °C at	
Decomposition	:	yes	
Method	:		
Year	:		
GLP	:		
Test substance	:		
Source	:	Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995			(28)
Decomposition	:	yes	
Method	:		
Year	:		

2. Physico-Chemical Data

Id 64-67-5
Date 18.12.2003

GLP :
Test substance :

Remark : decomposes to ethyl ether, ethylene and sulphur oxides at
temperatures above 100 degrees C.
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (38)

2.3 DENSITY

Type : density
Value : = 1.1774 - g/cm³ at 20 °C

Reliability : (2) valid with restrictions
03.11.2003 (6)

Type : relative density
Value : 1.1795 - at 20 °C
Method :
Year :
GLP : no data
Test substance :

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (38)

Type : relative density
Value : 1.172 - at 28 °C
Method :
Year :
GLP : no data
Test substance :

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (28)

Type : density
Value : 1.1803 - at °C
Method :
Year :
GLP : no data
Test substance :

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (22)

2.3.1 GRANULOMETRY

2. Physico-Chemical Data

Id 64-67-5

Date 18.12.2003

2.4 VAPOUR PRESSURE

Value : = .19078 - hPa at 20 °C
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.11.2003 (27)

Value : .13 - hPa at 20 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance :
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (38)

Value : .25 - hPa at 20 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance :
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (22)

Value : 1.33 - hPa at 47 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance :
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (28)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 1.14 - at °C
pH value : -
Method : other (calculated): EPIWIN (v 3.11) KOWWIN Submodel (v 1.67)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg): 0.14344;
Boiling point (deg C): 208.0; and
Melting point (deg C): -24.50.

2. Physico-Chemical Data

Id 64-67-5

Date 18.12.2003

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.12.2003 (31)

Partition coefficient :
Log pow : 1.14 - at °C
pH value : -
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
07.11.2003 (37)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 7000 - mg/l at 20 °C
pH value : -
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (15)

Solubility in : Water
Value : - at °C
pH value : -
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : Insoluble, decomposes at room temperature.
Reliability : (2) valid with restrictions
25.11.2003 (6)

Remark : 0.7% by weight solubility in water at 20 degrees C. Diethyl sulphate reacts vigorously with water.
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
09.10.2003 (38)

Remark : Practically insoluble in water and gradually decomposed by it. Rapidly decomposition by hot water into monoethyl sulfate and alcohol.
Source : Union Carbide Benelux Antwerpen

2. Physico-Chemical Data

Id 64-67-5
Date 18.12.2003

23.10.1995 ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston (28)

Remark : Insoluble in water.
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (22)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : 104 °C
Type : closed cup
Method : other: Tag Closed Cup (ASTM D 56)
Year :
GLP : no data
Test substance :
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (22) (28) (38)

2.8 AUTO FLAMMABILITY

Value : 436 - °C at
Method :
Year :
GLP : no data
Test substance :
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995 (22)

2.9 FLAMMABILITY

Result : other: no data to report
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
23.10.1995

2.10 EXPLOSIVE PROPERTIES

Remark : Flammability limits in air (% by weight):
- lower: 4.1

2. Physico-Chemical Data

Id 64-67-5
Date 18.12.2003

Source	: - upper: not determined Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(39)

2.11 OXIDIZING PROPERTIES

Result	: other: no data to report	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Remark	: vapour density (air = 1): 5.3	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(38)

3. Environmental Fate and Pathways

Id 64-67-5
Date 18.12.2003

3.1.1 PHOTODEGRADATION

DIRECT PHOTOLYSIS

Half-life t_{1/2} : = 6.5 - day(s)
Degradation : - % after
Quantum yield :
Deg. product :
Method : other (calculated): EPIWIN (v 3.11) AOP Submodel (v 1.91)
Year : 2003
GLP :
Test substance :

Remark : Overall OH rate constant = 1.6422 E-12 cm³/molecule/sec
The EPIWIN model was run using the following measured physical chemical properties:

Vapor pressure (mm Hg): 0.14344;

Boiling point (deg C): 208.0; and

Melting point (deg C): -24.50.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

15.12.2003

(29)

Remark : Nihil
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

06.10.2003

3.1.2 STABILITY IN WATER

Remark : Decomposes gradually to alcohol and sulfuric acid.
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995

Deg. products : 64-17-5 Ethanol
7664-93-9 Sulfuric acid

12.11.2003

(6)

3.1.3 STABILITY IN SOIL

Remark : Decomposes gradually by reaction with moisture in soil to alcohol and sulfuric acid

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995

3. Environmental Fate and Pathways

Id 64-67-5

Date 18.12.2003

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media : other: air (emissions to compartment = 1000 kg/hr)
Method : Calculation according Mackay, Level III
Year : 2003

Method : Equilibrium Concentration Model (EQC) Level III
Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg): 0.14344;
Boiling point (deg C): 208.0; and
Melting point (deg C): -24.50.

Result : Concentration (%):
Air - 77
Water - 15
Soil - 9
Sediment - < 0.1

Level III Fugacity Model (Full-Output):

=====

Chem Name : Sulfuric acid, diethyl ester
Molecular Wt: 154.18
Henry's LC : 8.4e-006 atm-m3/mole (Henry database)
Vapor Press : 0.143 mm Hg (user-entered)
Log Kow : 1.14 (Kowwin program)
Soil Koc : 5.66 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	76.6	143	1000
Water	14.7	360	0
Soil	8.7	360	0
Sediment	0.0274	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.01e-010	311	639	31.1	63.9
Water	3.34e-012	23.6	12.3	2.36	1.23
Soil	5.04e-011	14	0	1.4	0
Sediment	2.74e-012	0.011	0.000458	0.0011	4.58e-005

Persistence Time: 83.5 hr
Reaction Time: 240 hr
Advection Time: 128 hr
Percent Reacted: 34.8
Percent Advected: 65.2

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 142.6
Water: 360

3. Environmental Fate and Pathways

Id 64-67-5

Date 18.12.2003

Soil: 360
Sediment: 1440
Biowin estimate: 2.858 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Reliability Flag : (2) valid with restrictions
: Critical study for SIDS endpoint
15.12.2003 (32)

Media : other: water (emissions to compartment = 1000 kg/hr)
Method : Calculation according Mackay, Level III
Year : 2003

Method Remark : Equilibrium Concentration Model (EQC) Level III
: The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg): 0.14344;
Boiling point (deg C): 208.0; and
Melting point (deg C): -24.50.

Result : Concentration (%):
Air - < 1
Water - 99
Soil - < 0.1
Sediment - < 1

Level III Fugacity Model (Full-Output):

Chem Name : Sulfuric acid, diethyl ester
Molecular Wt: 154.18
Henry's LC : 8.4e-006 atm-m3/mole (Henry database)
Vapor Press : 0.143 mm Hg (user-entered)
Log Kow : 1.14 (Kowwin program)
Soil Koc : 5.66 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.527	143	0
Water	99.2	360	1000
Soil	0.0598	360	0
Sediment	0.185	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	2.8e-012	8.58	17.7	0.858	1.77
Water	9.06e-011	640	333	64	33.3
Soil	1.39e-012	0.386	0	0.0386	0
Sediment	7.44e-011	0.298	0.0124	0.0298	0.00124

Persistence Time: 335 hr
Reaction Time: 516 hr
Advection Time: 957 hr
Percent Reacted: 65
Percent Advected: 35

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 142.6
Water: 360
Soil: 360
Sediment: 1440

3. Environmental Fate and Pathways

Id 64-67-5

Date 18.12.2003

Biowin estimate: 2.858 (weeks)

Advection Times (hr):

Air: 100

Water: 1000

Sediment: 5e+004

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.12.2003

(32)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other: microbial seed
Contact time :
Degradation : 57 - (±) % after 20 day(s)
Result :
Kinetic of testsubst. : 5 day(s) 25 - %
10 day(s) 30 - %
20 day(s) 57 - %
- %
- %

Deg. product :
Method : other: BOD20
Year : 1974
GLP : no
Test substance :

Remark : The test method utilized was: "Standard Methods for the Examination of Water and Wastewater." 1971. 13th edition, Amer. Pub. Health Assn., New York, NY. A settled domestic wastewater was filtered through glass wool and then added (3 ml/bottle) as seed material to clean 300 ml BOD bottles. The dilution water was sparged with pure oxygen to produce an available DO level of 30 to 35 mg/l and added to the seed material to completely fill the bottles. The pure chemical was added to each bottle (3.0 µl/bottle) to provide a concentration of approximately 10 mg/l. At least two of the concentrations were tested in duplicate. Dissolved oxygen content was measured approximately five times throughout the test using a commercial DO meter filled with an agitated probe. When the DO level dropped below 4.0 mg/l, the contents were reaerated. Samples (2 ml) were analyzed routinely for nitrites and nitrates throughout the study because ammonia nitrogen and organic nitrogen contained in the test system could be oxidized to form these two compounds. No attempt was made to inhibit nitrification. Appropriately seeded blanks and glucose standards were prepared during each test run using the same dilution water used for the test samples.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
13.11.2003

(20) (40)

3.6 BOD5, COD OR BOD5/COD RATIO

3. Environmental Fate and Pathways

Id 64-67-5

Date 18.12.2003

COD
Method : other
Year :
COD : 1.25 mg/g substance
GLP :

Remark : calculated THOD
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995

(37)

3.7 BIOACCUMULATION

Remark : Based on the estimated Log Kow of 1.14 and the rapid hydrolysis of DES in water, the bioaccumulation potential is considered to be very low.
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

17.12.2003

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type :
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 95 -
Limit test :
Analytical monitoring : no data

Remark : test references:
(1) Methods for Measuring the Acute Toxicity of Effluents to Freshwater and Marine Organisms, EPA/600/4-85/013, March 1985.
(2) Annual Book of ASTM standards, Water and Environmental Technology, Vol. 111.04, (1990).

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

09.12.2003 (41)

Type :
Species : Salmo gairdneri (Fish, estuary, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 20 -
Limit test :
Analytical monitoring : no data
Method : other
Year : 1988
GLP : no data
Test substance : no data

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

23.10.1995 (18)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Species : Daphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 742.393 - calculated
Method : other: EPIWIN (v 3.11) ECOSAR Submodel (v 0.99g)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg): 0.14344;
Boiling point (deg C): 208.0; and
Melting point (deg C): -24.50.

15.12.2003 (30)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae:Green algae
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 5.192 - calculated
Method : other: EPIWIN (v 3.11) ECOSAR Submodel (v 0.99g)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg): 0.14344;
Boiling point (deg C): 208.0; and
Melting point (deg C): -24.50.

15.12.2003

(30)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	: LD50
Value	: 880 - mg/kg bw
Species	: rat
Strain	:
Sex	:
Number of animals	:
Vehicle	:
Doses	:
Method	: other: acute oral toxicity
Year	: 1949
GLP	: no
Test substance	: as prescribed by 1.1 - 1.4
Remark	: Rat strain was Wistar or Sherman. Six animals per dose group were dosed with the test substance. LD50 value is calculated using the method of Thompson, W. R. (1947. Use of moving averages and interpolation to estimate median-effective dose. Bact. Reviews, 11:115)
Result	: 95% confidence limits: 760-1010 mg/kg.
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
Test substance	: Test substance administered as a 10% solution in corn oil.
Reliability	: (2) valid with restrictions
Flag	: Critical study for SIDS endpoint
04.11.2003	(24)

5.1.2 ACUTE INHALATION TOXICITY

Type	: LC50
Value	: 250 - 500 ppm
Species	: rat
Strain	:
Sex	:
Number of animals	: 12
Vehicle	:
Doses	:
Exposure time	: 4 hour(s)
Method	: other
Year	: 1949
GLP	: no
Test substance	: as prescribed by 1.1 - 1.4
Remark	: 0/6 killed at 250 ppm; 6/6 killed at 500 ppm
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
Reliability	: (2) valid with restrictions
Flag	: Critical study for SIDS endpoint
17.12.2003	(24)

5. Toxicity

Id 64-67-5

Date 18.12.2003

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : 706 - mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: acute dermal toxicity
Year : 1951
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Original data reported as 600 ml/kg; 95% confidence for
value = 430-840 ml/kg; LD50 calculated based on density of 1.1774 g/ml.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.11.2003 (35)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : 350 - mg/kg bw
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : s.c.
Exposure time :
Method : no data
Year :
GLP : no data
Test substance : no data
Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston
01.10.2003 (42)

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals : 5
Vehicle :
PDII :
Result : irritating
Classification :
Method : Draize Test

5. Toxicity

Id 64-67-5

Date 18.12.2003

Year	: 1949	
GLP	: no	
Test substance	: as prescribed by 1.1 - 1.4	
Remark	: Application: 11mg (0.01 ml) applied to the clipped abdomen - the application site remained uncovered and was observed 24 hr after application.	
Result	: necrosis observed	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
04.11.2003		(24)
Species	: rabbit	
Concentration	: undiluted	
Exposure	:	
Exposure time	: 4 hour(s)	
Number of animals	: 6	
Vehicle	:	
PDII	:	
Result	: irritating	
Classification	:	
Method	: other: USDOT Skin Irritancy Test (Modified)	
Year	: 1982	
GLP	: no data	
Test substance	: as prescribed by 1.1 - 1.4	
Remark	: Application period: 4hr, 589 mg (0.5ml, undiluted test substance) covered. Both the skin and the gauze patch were moistened with saline before the test substance was applied. Skin reactions were recorded according to the system of Draize at one hour, one day and two days after application.	
Result	: 4/6 with ecchymosis and slight to severe edema, 2/6 with erythema and slight to severe edema, none had necrosis.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
Conclusion	: not corrosive	
04.11.2003		(33)

5.2.2 EYE IRRITATION

Species	: rabbit
Concentration	: undiluted
Dose	:
Exposure time	:
Comment	:
Number of animals	: 1
Vehicle	:
Result	: irritating
Classification	: risk of serious damage to eyes
Method	: other
Year	: 1949
GLP	: no
Test substance	: as prescribed by 1.1 - 1.4
Remark	: Method: see Carpenter,C.P. and Smyth,H.F.(1946), Am.J.Ophtal. 29:1363-1372; and Smyth,H.F. and Carpenter,C.P.(1944), J.Ind.Hyg.Toxicol. 26:269-273. Volumes installed: 0.001, 0.005, 0.02ml (1.18, 5.9,

5. Toxicity

Id 64-67-5

Date 18.12.2003

Result	: 23.6 mg) applied directly to the cornea.
Source	: Severe corneal injury.
	: Union Carbide Benelux Antwerpen
	: ECB - Existing Chemicals Ispra (VA)
	: UNION CARBIDE CORPORATION Houston
04.11.2003	(24)

5.3 SENSITIZATION

Remark	: No information available.
Source	: Union Carbide Benelux Antwerpen
	: ECB - Existing Chemicals Ispra (VA)
	: UNION CARBIDE CORPORATION Houston
23.10.1995	

5.4 REPEATED DOSE TOXICITY

Remark	: See section 5.7
Source	: Union Carbide Benelux Antwerpen
	: ECB - Existing Chemicals Ispra (VA)
	: UNION CARBIDE CORPORATION Houston
23.10.1995	

5.5 GENETIC TOXICITY 'IN VITRO'

Type	: Salmonella typhimurium reverse mutation assay
System of testing	: TA100
Test concentration	: 500, 1000, 2000, and 4000 µg/plate
Cycotoxic concentr.	: None
Metabolic activation	: without
Result	: positive
Method	: other
Year	: 1992
GLP	: no data
Test substance	: as prescribed by 1.1 - 1.4
Method	: This assay was carried out with S. typhimurium TA100 in the absence of S9 mixture using the preincubation method (Maron, D.M. and B.N. Ames. 1983. Revised methods for the Salmonella mutagenicity test, Mutation Res., 113:173-215). The reaction mixture consisted of 0.5 ml of phosphate buffer, 0.1 ml of a solution of the test substance prepared at gradient concentration, and 0.1 ml of the cell suspension grown for 8 h at 37 C. Dose concentrations ranged from 500 to 4000 µg/plate. Duplicate plates were run at each dose level for the test substance and solvent controls. A confirmatory assay also was conducted. The test was considered positive when the number of revertant colonies (mean value of two plates) was more than twice that of the solvent control in a dose-dependant manner and the reproducibility of the results was confirmed by a second assay.
Result	: In this study, the mutagenicity of diethyl sulfate was demonstrated using a preincubation reverse assay in S. typhimurium TA100 without any metabolic activation. The results of the test showed a dose-dependent increase in the number of revertant colonies that was more than twice the solvent control.

	Dose (µg/plate)	His+ revertants/plate																																																							
	0 (solvent control)	136 ± 5																																																							
	500	138 ± 4																																																							
	1000	834 ± 1																																																							
	2000	4801 ± 48																																																							
	4000	4261 ± 81																																																							
	Note: results are the mean ± SD of counts from duplicate plates.																																																								
Source	: UNION CARBIDE CORPORATION Houston																																																								
Reliability	: (2) valid with restrictions																																																								
Flag	: Critical study for SIDS endpoint																																																								
17.11.2003	(19)																																																								
Type	: HGPRT assay																																																								
System of testing	: Chinese Hamster Ovary (CHO) cells																																																								
Test concentration	: 0.08% by volume without S9 activation, 0.04% by volume with S9 activation																																																								
Cycotoxic concentr.	:																																																								
Metabolic activation	: with and without																																																								
Result	: positive																																																								
Method	: other																																																								
Year	: 1980																																																								
GLP	: no																																																								
Test substance	: as prescribed by 1.1 - 1.4																																																								
Method	: CHO cells were exposed for 5 hours to five concentrations of diethyl sulfate from 0.08% (by volume) without the addition of an S9 metabolic activation system and from 0.04% to 0.0025% with S9 activation. In a second, repeat test identical concentrations were tested with S9, and one additional, lower concentration (0.0025%) was tested without S9 activation. Dilutions of diethyl sulfate for testing were prepared by either direct addition of the test agent into the cell culture media or by making sequential one-half dilutions in glass distilled DMSO. The surviving fraction was determined at 20 to 24 hours after treatment and the mutant fraction was determined after a 7 to 10 day period to allow "expression" of the mutant phenotype. S9 liver homogenate was prepared from Aroclor 1254-induced Sprague-Dawley male rats. Appropriate dose levels of positive, negative (deionized water) and solvent (DMSO) controls were used.																																																								
Result	: An apparent dose response effect upon cytotoxicity was observed for the concentrations of test substance tested with or without S9 activation in comparison to the values for the solvent or negative controls; although a slight difference in cytotoxicity was seen in the two experiments. The following table provides the percent survival data for the two independent experiments:																																																								
	<table><tr><td></td><td colspan="2">Experiment 1</td><td colspan="2">Experiment 2</td></tr><tr><td>Concentration</td><td colspan="2">% Survival</td><td colspan="2">% Survival</td></tr><tr><td>(%, v/v)</td><td>-S9</td><td>+S9</td><td>-S9</td><td>+S9</td></tr><tr><td>0.080</td><td>0</td><td>(NT)</td><td>0</td><td>(NT)</td></tr><tr><td>0.040</td><td>3.0</td><td>0.1</td><td>14.0</td><td>2.1</td></tr><tr><td>0.020</td><td>18.8</td><td>3.0</td><td>34.0</td><td>39.2</td></tr><tr><td>0.010</td><td>31.2</td><td>11.0</td><td>51.5</td><td>45.5</td></tr><tr><td>0.005</td><td>36.0</td><td>24.2</td><td>55.5</td><td>57.5</td></tr><tr><td>0.0025</td><td>(NT)</td><td>31.0</td><td>53.2</td><td>51.0</td></tr><tr><td>DMSO control</td><td>45.5</td><td>43.8</td><td>52.5</td><td>47.8</td></tr><tr><td>Neg. control</td><td>47.8</td><td>35.0</td><td>37.0</td><td>67.0</td></tr></table>			Experiment 1		Experiment 2		Concentration	% Survival		% Survival		(%, v/v)	-S9	+S9	-S9	+S9	0.080	0	(NT)	0	(NT)	0.040	3.0	0.1	14.0	2.1	0.020	18.8	3.0	34.0	39.2	0.010	31.2	11.0	51.5	45.5	0.005	36.0	24.2	55.5	57.5	0.0025	(NT)	31.0	53.2	51.0	DMSO control	45.5	43.8	52.5	47.8	Neg. control	47.8	35.0	37.0	67.0
	Experiment 1		Experiment 2																																																						
Concentration	% Survival		% Survival																																																						
(%, v/v)	-S9	+S9	-S9	+S9																																																					
0.080	0	(NT)	0	(NT)																																																					
0.040	3.0	0.1	14.0	2.1																																																					
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0.010	31.2	11.0	51.5	45.5																																																					
0.005	36.0	24.2	55.5	57.5																																																					
0.0025	(NT)	31.0	53.2	51.0																																																					
DMSO control	45.5	43.8	52.5	47.8																																																					
Neg. control	47.8	35.0	37.0	67.0																																																					
	(NT) = Not Tested																																																								

Significant increases in the mutant frequency were obtained which indicated a dose-related induction of the frequency of mutants/10⁶ viable cells over the 16-fold range of concentrations tested for potential mutagenic action either

with or without the presence of an S9 metabolic activation system. All tested concentrations of diethyl sulfate produced an increase in the mutation frequency which was statistically significant from the concurrent solvent control in the test either with or without S9 activation. These significant mutagenicity data were considered to be a biologically significant indication of a positive effect. The data also indicated the presence of a dose-related increase in the number of mutants induced by treatment which is considered an important criterion of a positive mutagenic response. Diethyl sulfate was considered to be a mutagenic agent based upon the data. The following table provides the mutant frequency results with and without S9 activation:

Concentration (%, v/v)	Experiment 1 Mutants (a)		Experiment 2 Mutants (a)	
	-S9	+S9	-S9	+S9
0.08	382.2*	(NT)	TOXIC	(NT)
0.04	1385.9*	663.3*	811.1*	1267.3*
0.02	672.9*	951.2*	1021.8*	770.7*
0.01	525.3*	472.7*	432.7*	699.0*
0.005	332.7*	131.2*	303.4*	598.0*
0.0025	(NT)	289.2*	198.4	273.7*
DMSO control	88.6	50.7	123.4	35.5
Neg. control	170.3*	73.9	18.7	57.5

(a) = Total # mutant colonies per 10^6 cells plated divided by viable fraction.

* Significantly different from DMSO control ($p < 0.05$, Student's t-test)

Source
11.11.2003

: UNION CARBIDE CORPORATION Houston

(36)

Type
System of testing
Test concentration
Cycotoxic concentr.
Metabolic activation
Result
Method
Year
GLP
Test substance

: Sister chromatid exchange assay
: Chinese Hamster Ovary (CHO) cells
: 0.02% to 0.00125%
: 0.02%
: without
: positive
: other
: 1980
: no
: as prescribed by 1.1 - 1.4

Method

: Dilutions of diethyl sulfate for testing, ranging from 0.02% to 0.00125% (by volume), were prepared either by direct addition into the culture medium or by making sequential one-half dilutions of the maximum dose level in DMSO. For determination of direct mutagenic action, CHO cells were exposed to diethyl sulfate and appropriate controls for 5 hours without S9 activation. Indirect mutagenic action requiring metabolic activation by liver S9 homogenate, was not studied because of the highly significant positive responses observed in the experiment without S9. Chemicals which produce a highly significant response by direct action are considered mutagenic regardless of the response obtained with S9. BrdU required to differentiate between the individual "sister" chromatids by SCE staining, was present at a concentration of 3 $\mu\text{g/mL}$ in the growth medium during treatment and during the culture period following exposure. A total of 15 cells/dose level and 5 dose levels, without metabolic activation were examined. Appropriate dose levels of positive, negative (deionized water) and solvent (DMSO) controls were used. Ethylmethanesulfonate was used as the positive control substance

Result

- without metabolic activation.
- : A statistically-significant increase in the SCE frequency was produced by two of the dose-levels of diethyl sulfate tested for direct action in the absence of a metabolic activation system. The test without S9 activation was considered a positive indication of potential direct mutagenic action of diethyl sulfate. An increase in the frequency of SCE corresponding to increased dose-levels of diethyl sulfate was readily apparent from 0.00125% to 0.01% which indicated a probable biological significance of these results. The 0.02% concentration was cytotoxic and inhibited the appearance of cells with SCE staining, possibly because of effects of the test agent on cell growth. The sample of diethyl sulfate was classified as a positive mutagenic agent by direct action and testing with an S9 activation system was not performed. Treatments of CHO cells with diethyl sulfate over a 16-fold range of concentrations indicated a significant potential for mutagenic activity in tests of direct mutagenic action without addition of an active S9, metabolic activation system. Evidence of a dose-related effect of diethyl sulfate exposure on the SCE frequency was evident and the test agent was considered to be an active agent in the in vitro assay. Following is a table of results:

Concentration (%, v/v)	Mean number of SCE/chromosome (+/- S.D.)
0.020	0.474 (0.130) @
0.010	2.192 (0.825)*
0.005	1.634 (0.478)*
0.0025	1.032 (0.277)
0.00125	0.868 (0.287)

DMSO control 0.871 (0.304)

Negative control 0.668 (0.125)

@ = Toxic, only 9 analyzable cells found

* = Significantly different from DMSO control (p<0.05, Student's t-test).

Source**Reliability**

11.11.2003

- : UNION CARBIDE CORPORATION Houston
- : (1) valid without restriction

(36)

Type**System of testing****Test concentration****Cycotoxic concentr.****Metabolic activation****Result****Method****Year****GLP****Test substance**

- : Unscheduled DNA synthesis
- : rat hepatocyte cells
- : 100 x 10⁻³% to 0.1 x 10⁻³% by volume
- :
- : no data
- : positive
- : other
- : 1980
- : no
- : as prescribed by 1.1 - 1.4

Method

- : Induction of DNA damage in rat liver cells (hepatocytes), resulting in stimulation of Unscheduled DNA Synthesis (UDS), was studied at a minimum of six dose levels which spanned a 1000-fold range of concentrations from 0.0001, 0.001, 0.003, 0.01, 0.03, and 0.1% (v/v). Cells were treated with diethyl sulfate for 2 hours in culture medium containing 3H-thymidine, hydroxyurea and appropriate dilutions of diethyl sulfate prepared in DMSO. Determination of UDS activity was performed by analyses of radioactive incorporation into isolated hepatocytes nuclei or in DNA. Appropriate dose levels of positive, negative (deionized water) and solvent (DMSO) controls were used.
- : Diethyl sulfate stimulated a significant amount of

Result

incorporation of radioactive thymidine in cells treated over a 1000-fold range of all test concentrations. Measurements of radioactive incorporation into either nuclei or DNA isolated and precipitated from aliquots of nuclei from the same populations of treated cells verified the activity of the positive control agents and the significant activity of the diethyl sulfate test sample. Diethyl sulfate was considered an active mutagenic agent in the test with hepatocytes.

% v/v Concentration	Radioactivity % of solvent control
0.1	193
0.03	312
0.01	260
0.003	281
0.001	191
0.0001	321

Source : UNION CARBIDE CORPORATION Houston
Reliability : (1) valid without restriction
 13.11.2003

(36)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : other: ddY
Route of admin. : i.p.
Exposure period : one day
Doses : 100, 200, 400 mg/kg bw
Result : positive
Method : other
Year : 1992
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : 7 week old male ddY mice were used after 1 week acclimatization. They were given commercial food pellets and water ad libitum. The doses administered were decided by referring to published LD50s but in some cases by a preliminary dose-finding experiment. Three doses of the test substance were tested with 4 mice per group, by a single intraperitoneal injection, at 100, 200, and 400 mg/kg bw. Peripheral blood (5 µl) was collected from a tail blood vessel. One thousand well-stained reticulocytes/animal were examined. The data at 48 hours were analyzed with Fisher's exact test to test the significance of the frequency of micronucleated reticulocytes (MNRET) at each test dose compared with the control data, which was the total MNRETs of 12 mice at 0 hours (before treatment). The significance level was 0.01.

Result : MNRET induction was observed only at the highest dose of DES (400 mg/kg bw). The following table summarizes the results:

Single dose (mg/kg)	Time (hours) after the last treatment (a)			
	0	24	48	72
0	0.13 ± 0.06			
100	0.10 ± 0.00	0.20 ± 0.14	0.25 ± 0.17	0.13 ± 0.05
200	0.13 ± 0.05	0.25 ± 0.13	0.28 ± 0.17	0.18 ± 0.10
400	0.15 ± 0.10	0.28 ± 0.06	0.50 ± 0.10*	0.17 ± 0.06

(a) Values represent mean MNRET induction of four mice per dose group ±

5. Toxicity

Id 64-67-5

Date 18.12.2003

SD.

* Significantly different from 0 hour, $p < 0.01$.

Source : UNION CARBIDE CORPORATION Houston
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
 14.11.2003

(1)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : other: MS/Ae
Route of admin. : i.p.
Exposure period : 2 days
Doses : 80 and 160 mg/kg
Result : positive
Method : other
Year : 1995
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance was administered by i.p. injection in olive oil. Diethyl sulfate was given twice, 24 h apart, to MS/AE mice at 10 ml/kg. Peripheral blood was collected at time 0 (before treatment) and at 6 h intervals, 24 after the second treatment.

Result : Dose at MN/1000 RET's
 a time Sampling # of assessed per Group Mean
 (mg/kg) time (h) animals animal ± SD (%)
 DS (160) 0 5 2 3 2 4 4 3.0 ± 1.0
 24 4 5 9 9 12 8.8 ± 2.9
 30 4 15 20 15 12 15.5 ± 3.3
 36 4 14 13 10 16 13.3 ± 2.5
 42 4 11 12 8 8 9.8 ± 2.1
 48 4 12 7 7 9 8.8 ± 2.4
 54 4 7 8 7 5 6.8 ± 1.3
 60 4 2 2 5 2 2.8 ± 1.5
 DS (80) 0 5 3 3 2 6 2 3.2 ± 1.6
 24 5 11 7 9 7 9 8.6 ± 1.7
 30 5 18 8 6 7 6 9.0 ± 5.1
 36 5 10 6 7 5 9 7.4 ± 2.1
 42 5 8 6 4 3 7 5.6 ± 2.1
 48 5 6 2 1 3 2 2.8 ± 1.9
 54 5 2 6 3 0 0 2.2 ± 2.5
 60 5 5 3 0 1 2 2.2 ± 1.9

The test substance showed peak MNRET (immature erythrocyte with a micronucleus) responses at 30 hours.

Source : UNION CARBIDE CORPORATION Houston
 14.11.2003

(7)

Type : Dominant lethal assay
Species : mouse
Sex : male
Strain : other: 101/E1 x C3H/E1
Route of admin. : i.p.
Exposure period : single injection
Doses : 0, 100, 200, 300 mg/kg
Result :
Method : other: rodent Dominant lethal test
Year : 1988
GLP : no data
Test substance : no data

5. Toxicity

Id 64-67-5

Date 18.12.2003

- Remark** : 25 mice/group; animals 80-98 days old at time of treatment and initial mating. Males were caged with individual F1 hybrid females for 4 day intervals for 48 days for a total of 12 mating intervals.
intraperitoneal injection
- Result** : Positive; significantly increased pre- and post-implantation loss observed in the 200 mg/kg and 300 mg/kg groups. There was a non-significant increase in pre-implantation loss for the 100 mg/kg group.
- Source** : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

11.11.2003

(5)

- Type** : Dominant lethal assay
- Species** : mouse
- Sex** : male
- Strain** : C57BL
- Route of admin.** : other: intrascrotal injection
- Exposure period** : single injection
- Doses** : 0, 6.0, 30, 150 mg/kg
- Result** :
- Method** : other: rodent dominant lethal test
- Year** : 1971
- GLP** : no data
- Test substance** : no data

- Remark** : 15 male mice/group (Strain: C57BL/B6); animals 2.5-3.0 months of age. Test substance administered in physiological saline solution. Each male mated with three virgin CBA females immediately after injection; females replaced each week for six weeks. At the sixth week, three to four females were used for the mating. CBA females were killed on days 14-17 of gestation and examined for embryonic lethality. The number of live embryos (A), dead embryos (B) and the number of corpora lutea (C) were counted. The following indices were calculated:
- 1) death rate before implantation = $C - (A+B)/C$
 - 2) death rate after implantation = $B/A+B$
 - 3) survival = A/C .

The relative indices were calculated by dividing the indices of the experimental group by the corresponding index in the control group. The significance of the differences between the experimental and control indices was determined by the chi square method.

- Result** : Positive at doses of 6.0 and 150 mg/kg.
The following table summarizes the indices relative to the control values:

Dose mg/kg	Week	Fertile Females (%)	Relative Lethality (%)		Relative Survival Rate (%)
			Before Implantation	After Implantation	
150	1	31	171.1*	100.0	90.5
	2	67	170.0*	131.3	84.2*
	3	88	138.4	214.0*	86.2
	4	100	132.4	151.4	91.5
	5	118	107.1	153.9	93.5
	6	89	95.1	82.0	102.3
30	1	87	97.4	143.4	96.8
	2	92	109.4	113.7	96.7
	3	118	65.3	140.4	104.5
	4	125	94.3	135.7	98.2
	5	130	80.7	122.4	101.6
	6	99	113.6	134.7	94.3
6	1	91	161.8*	152.6	87.8*

2	77	178.7*	144.1	79.8*
3	129	92.2	152.6	95.3
4	111	128.9	115.7	94.1
5	118	66.4	189.4*	98.3
6	99	81.5	134.7	101.2

* Significantly different from control.

The following table summarizes the data for the first five weeks of the study, reflecting the sensitivity of the meiotic and postmeiotic stages of spermatogenesis. Data are represented relative to the control values.

Dose mg/kg	Relative Lethality (%) After Implantation	Relative Survival (%)
150	157.1*	89.0*
30	128.5	100.0
6	157.1*	92.3*

* Significantly different from control.

At these stages, the doses of 6 and 150 mg/kg caused almost the same frequency of dominant lethal mutations. There was no change in the incidence of fertility of the males at the sixth week at any dose level tested.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

14.11.2003

(14)

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : male
Strain : other: Samarkand
Route of admin. : oral feed
Exposure period : 2.5-3.0 hours
Doses : 10.5%, 0.75% solutions
Result :
Method : other: SLRL test
Year : 1978
GLP : no data
Test substance : no data

Remark : (modified test)
Test substance administered to males in 5% glucose feeding solution; males mated to Oregon K virgin females immediately after feeding treatment. After mating, females were allowed to oviposit immediately or were held for 6 days prior to ovipositing.

Embryonic lethality was determined by determining the incidence of unhatched eggs after 24 and 48 hours. Post embryonic lethality was determined by scoring the incidence of larval or pupal death in eggs that had hatched.

Result : Positive. Dose-dependent increase in embryonic lethality; holding DES-exposed sperm for 6 days prior to oviposition resulted in a marked increase in post-embryonic lethality over controls and non-stored DES-exposed sperm.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

17.12.2003

(16)

Type : other: DNA base sequence changes
Species : Drosophila melanogaster
Sex : male
Strain : no data

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Route of admin. : oral feed
Exposure period : 3 hours (oral feeding)
Doses : 10, 15, 25 mM (oral feeding), 6.25 mM (injection)
Result :
Method : other: postmeiotic germ cell mutation assay in *Drosophila melanogaster*
Year : 1993
GLP : no data
Test substance : no data

Remark : oral, injection
Test substance administered to males in buffered 5% sucrose feeding solution or injected in 0.7% NaCl vehicle (0.2 ul). F1 and F2 progeny were screened for occurrence of the vermillion (v) mutation. DNA from 1 g flies was isolated and the vermillion gene amplified using polymerase chain reaction (PCR).

Result : Base pair substitutions (93%) and deletions (7%) were induced by treatment with diethyl sulphate; 31 transmissiblevermillion mutants were recovered in F1 and F2 progeny. The most frequent type of alteration were GC -AT transitions and AT -TA transversions.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

17.09.2003

(23)

5.7 CARCINOGENICITY

Species : mouse
Sex : male
Strain : other: C3H/HeJ
Route of admin. : dermal
Exposure period : lifespan
Frequency of treatm. : 3x/week
Post exposure period : none
Doses : 1 brushful per mouse, approximately 7.4 mg/mouse/application
Result : positive
Control group : yes, concurrent vehicle
Method : other: dermal carcinogenicity
Year : 1976
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Three groups of 40 animals each were exposed to the undiluted test substance, vehicle or positive control substance three times per week via non-occluded application to the clipped back. The animals in the test group were exposed to the undiluted test substance at an average dose of 7.4 mg/mouse/application; animals in the vehicle control group were exposed to acetone at an average dose of 12.6 mg/mouse/application and the animals in the positive control group were exposed to methylcholanthrene (as a 0.2% dilution in benzene) at an average dose of 0.033 mg/mouse/application. The test and control substances were applied to each animal with a series 197, number 1 Grumbacher brush. All animals were 8-9 weeks of age at study initiation. Dosing continued until all surviving mice within a group were observed grossly with malignant skin neoplasms or for their lifespan. Dosing was terminated after 22 months in the diethyl sulfate group; after 6 months in the positive control group; and animals in the vehicle control group were dosed for their lifetime.

Result : Repeated dermal application of undiluted diethyl sulphate produced malignant skin neoplasms in 21 mice out of a

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surviving effective group of 27 animals. Maximum survival time for the test group (22 months) was shorter than that of the vehicle control group (27 months); median latent period for appearance of neoplasms was 15.7 months for the test group, 3.7 months for positive control group; no tumors were observed in the vehicle control group.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
Reliability Flag	: (1) valid without restriction : Critical study for SIDS endpoint
03.11.2003	(34)
Species	: rat
Sex	: no data
Strain	: other: BD rats
Route of admin.	: gavage
Exposure period	: 81 weeks
Frequency of treatm.	: weekly
Post exposure period	:
Doses	: 25, 50 mg/kg
Result	:
Control group	: no
Method	: other: Carcinogenicity
Year	:
GLP	: no data
Test substance	: no data
Remark	: 12 animals/group; animals approximately 100 days old at start of treatment; survivors observed until death.
Result	: Benign papillomas of forestomach observed in 6/24 (number per group not specified); 2/24 squamous cell carcinoma of forestomach observed (one per group).
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
12.11.2003	(3) (8) (9)
Species	: rat
Sex	:
Strain	: other: BD rat
Route of admin.	: i.v.
Exposure period	: day 15 of gestation
Frequency of treatm.	: once
Post exposure period	:
Doses	: 85 mg/kg
Result	:
Control group	: no
Method	: other: transplacental carcinogenesis
Year	:
GLP	:
Test substance	: no data
Remark	: Maternal dose = 25% of fetal LD50. Three pregnant females injected with test substance on day 15 of gestation; test substance solubilized in an unspecified (probably arachis) oil. Offspring observed until death.
Result	: Neurogenic tumors observed in 3 of 30 surviving offspring.
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston
12.11.2003	(3) (4) (8) (9)

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Species : rat
Sex : no data
Strain : other: BD rats
Route of admin. : s.c.
Exposure period : 49 weeks
Frequency of treatm. : weekly
Post exposure period :
Doses : 25, 50 mg/kg
Result :
Control group : no
Method : other: Carcinogenicity
Year :
GLP : no data
Test substance : no data

Remark : 12 animals/group; test substance administered as 1.25% or 2.50% solutions in arachis oil. Animals approximately 100 days old at start of treatment; survivors observed until death.

Result : Local sarcomas observed at site of injection in 11 of survivors in high dose group with 2 metastases to the lung; there were local tumors in 6/12 rats in the 25 mg/kg group. Historical data indicated that arachis oil did not induce local tumors when injected subcutaneously.

Source : Union Carbide Benelux Antwerpen
ECB - Existing Chemicals Ispra (VA)
UNION CARBIDE CORPORATION Houston

04.11.2003

(3) (8) (9)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : Type: Cohort study.
A historical study examined cancer incidence in 335 process workers who had one or more months employment in an isopropanol plant and an ethanol plant between 1950 and 1976. A total of 225 were still alive, 48 were dead and 32 lost to follow-up. The SIR for laryngeal cancer in this cohort was 5.04, based on four cases. In an expanded cohort of 740 male workers, the SIR was 3.2 based on seven cases. Interviews of former and present supervisors indicated there were frequent exposures to diethyl sulphate, sulfur dioxide, and ethyl ether. The authors speculate that diethyl sulphate formed during the strong-acid process of ethanol production, may be the causative agent.

Source : Union Carbide Benelux Antwerpen

23.10.1995	ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	(13)
Remark	: Type: Cohort study A historical control study of the same worker population examined by Lynch found 50 cases of upper respiratory cancer, including 34 laryngeal cancers. It was determined that the greatest incidence of upper respiratory tract cancers occurred in workers exposed to high levels of sulphuric acid. Levels of diethyl sulphate were not measured.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(25)
Remark	: Type: Cohort study A mortality study examined the experience of 1031 ethanol and isopropanol production workers from two chemical plants. Workers were employed for one or more months between 1941 and 1978 were followed through 1983. Among workers exposed to the strong-acid process, there were two deaths from laryngeal cancers (SMR 2.00) and three from cancers of the buccal cavity and pharynx (SMR 1.36); the mortality rate for lung cancers was not elevated (SMR 0.94). No cancer deaths were seen among weak-acid process workers.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(26)
Remark	: Type: Case control study. Controls without cancer were individually matched to 17 gliomas deaths who had worked at a petrochemical plant between 1955-77. Possible associations between brain cancer and job title, department, history of chemical exposure, location within the plant, dates of employment, and place of residence were examined. Estimated exposure to diethyl sulphate gave an odds ratio of 2.1; duration of exposure was not related to disease status.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(12)
Remark	: Type: Case control study. Controls without cancer were matched to 21 brain cancer cases; 17 were gliomas previously analyzed of using different controls by Leffingwell et al. The proportion of brain cancer cases exposed to diethyl sulphate was determined to be similar to that of controls.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(2)

Method	: A Texas petrochemical plant had elevated standardized mortality ratios for neoplasms of the brain. A case-control study examined possible associations between gliomas of the brain and job title, departmental employment history, chemical exposure history, geographic location within plant, dates of employment, and residence. An earlier case control study had also been conducted on the same plant over the same issue.	
Remark Result	: Case-control study of Gliomas of the Brain : No significant differences between cases and controls were apparent in duration of exposure to any of these chemicals, of which many were used simultaneously. The greatest apparent risks were associated with exposure to carbon dioxide, diethyl sulfate, diethylene glycol, ethanol, ethylene, isopropanol, methane, tetraethylene glycol, and vinyl acetate with first employment in the 1940s or early 1950s, and with residence in La Marque, Texas.	
Source 16.09.2003	: UNION CARBIDE CORPORATION Houston	(21)
Method	: Cases consisted of 21 deaths in which the underlying cause was confirmed as a primary brain tumor. Two control groups of 80 employees each were randomly selected from 450 decedents known to the company in June, 1979. Potential exposures while employed were compared between cases and controls for five known or suspect carcinogens. Exposure potentials were also compared for an additional 37 chemicals to which at least four cases were potentially exposed. Overall and 15-year latency analyses were performed.	
Remark Result	: Case-control study of Chemical exposures and Brain tumors : 45.5% of the employees were exposed to the test substance of which 40.0% had gliomas. 48.6% and 40.6% were exposed to control 1 and 2, respectively. The proportion of cases exposed to the five potential carcinogenic chemicals were lower than or consistent with the proportion of exposed controls. No statistically significant differences between the proportions of cases and controls exposed to the 37 other chemicals were found. Exposure determinations could not be made for 48% to 57% of the cases and for 56% to 67% of the controls in each group. This was due to the high proportion of UCC Texas City employees who were assigned to maintenance departments where plantwide travel makes exposure to all chemicals theoretically possible, but technically unknown.	
Source 27.07.2000	: UNION CARBIDE CORPORATION Houston	(2)

5.11 ADDITIONAL REMARKS

Type	: Metabolism
Remark	: Following a single 1 ml subcutaneous, oral, or intraperitoneal administration of a 5% (v/v) diethyl sulphate solution in arachis oil (59 mg/rat), male rats were housed in metabolism cages and urine collected for 24 hours. Ethylmercapturic acid and a sulfoxide were detected in the urine of DES-treated rats by paper chromatography. The author propose a metabolic pathway involving glutathione conjugation with one ethyl group.

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Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
16.09.2003		(10)
Type	: other: DNA extraction and recovery	
Remark	: Exposure of HeLa cells in culture to 10 mM DES in 3% DMSO for 1 hour resulted in a 39.3% recovery of 3Hthymidine-labelled DNA after cold phenol extraction, when compared to non-treated control cells. Isolated DNA alkylated by DES shows multiple single-strand breaks and denatured DNA. Other techniques were also employed to demonstrate the presence of macromolecular DNA-protein complexes formed after alkylation with DES.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
23.10.1995		(11)
Type	: other: Toxicity to fertility	
Remark	: Diethyl sulphate damaged DNA of E.Coli at the concentration of 5umol/l. The substance damages DNA of Hamster ovary at the concentration of 2.5 mmol/l. The substance displayed mutagenicity to Hamster gene at the concentration of 1 mmol/l.	
Source	: Union Carbide Benelux Antwerpen ECB - Existing Chemicals Ispra (VA) UNION CARBIDE CORPORATION Houston	
16.09.2003		(17)

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7. Eff. Against Target Org. and Intended Uses

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7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT